

D-B.2

Methodological Handbooks & Toolkit for Clinical Practice Guidelines and Clinical Decision Support Tools for Rare Diseases

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GUIDELINES AND CLINICAL DECISION SUPPORT TOOLS

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Handbook #6: Methodology for the elaboration of Evidence
Reports for rare diseases



Authorship

Aragon Health Sciences Institute (IACS)

Authors

Celia Muñoz Fernández, BA in Economics.

Aragon Health Sciences Institute (IACS, Spain)

Patricia Gavín Benavent, MD, PhD.

Aragon Health Sciences Institute (IACS, Spain)

Internal Reviewers

María Bono Vega, BSc in Biochemistry.

Aragon Health Sciences Institute (IACS, Spain)

María Soledad Isern de Val, BSc in Biochemistry, PhD.

Aragon Health Sciences Institute (IACS, Spain)

Lucía Prieto Remón, BA in Business and Marketing.

Aragon Health Sciences Institute (IACS, Spain)

Collaborators

María Pilar Blas Diez, Information Specialist

Aragon Health Sciences Institute (IACS, Spain)

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Evidence Reports are systematic reviews that summarises the best available evidence on a topic. This handbook provides information on the main characteristics of these documents, how they should be planned, the structure of the working group and the key steps in their elaboration.

1. Background

With the launching of the first European Reference Network (ERN) in 2017, a care model based on the concentration of knowledge and resources in highly specialised care units for rare diseases became effective in Europe. As of today, 24 European Reference Network work co-ordinately and demand reliable and practical tools, like Clinical Practice Guidelines (CPG) and Clinical Decision Support Tools (CDST) to ensure the safest and most efficient care is provided to patients with rare diseases and carers through the EU.

Nonetheless, there are a number of challenges surrounding the development of CPG and CDST for rare diseases. One of the most relevant barrier is the lack of high-quality evidence, in which the foremost methodological frameworks like GRADE rely on ¹.

Therefore, there is a need for specific methodological approaches that can provide reliable and useful Clinical Practice Guidelines (CPGs) and Clinical Decision Support Tools (CDST) for rare diseases to be used by ERNs. The project also aims to provide a common methodology, in order to harmonise the elaboration process of CDST and CPGs in the ERNs.

1.1. Work Package B: Methodologies for CPGs and CDSTs for Rare Diseases

Work Package B of TENDER N°SANTE/2018/B3/030 pursues the development of methodologies for the prioritisation, appraisal, adaptation, development and implementation of CPGs and CDSTs for rare diseases.

The objective of WP-B of TENDER N°SANTE/2018/B3/030 entails two main steps: Firstly, an analysis of the state of the art on methodologies for CPGs and CDSTs for rare diseases, and secondly, the elaboration of methodological handbook and toolkit for the prioritisation, appraisal, adaptation, development and implementation of CPGs and CDSTs for rare diseases.

It is worth noting that within the scope of WP-B, “rare diseases” is the term used to refer to rare diseases as well as low prevalence complex diseases.

1.2. Context for Evidence Reports development in rare diseases

Evidence reports are systematic reviews that summarises the best available evidence on a topic. They are generally used by clinical professional organisations to support the development of clinical practice guidelines or by policy makers to inform their programme planning and research priorities.

1.3. The development process of Evidence Reports: Main Steps

TASK	•DEFINITION
Composition of the Working Group	•Bring together the profiles with the necessary knowledge for the development.
Planning and protocol elaboration	•Specification of the scope, objectives and methods that will be used for the development.
Literature search and identification of the evidence	•Selection of the information sources and define a search strategy for evidence identification.
Study selection and data extraction	•Selection of the studies to analyse according to the eligibility criteria defined previously.
Assess the certainty of the evidence and synthesis	•Quality and certainty of the body of evidence is evaluated and presented in a structured way.
Results and conclusions	•Present the information and highlight different factors that are relevant for evidence report users
External review	•Review process in order to enrich content, and increase external validity of the report.

2. Composition of the Working Group

Evidence Reports elaboration do not include formulation of recommendations for clinical practice. For this reason, it is recommended that the working group will be essentially technical. The expertise or profiles that may be necessary to carry out the elaboration are the following:

- An experienced medical/healthcare librarian or information specialist.
- Methodologists with a deep knowledge in critical appraisal.
- Methodologists with knowledge and experience in performing quantitative evidence syntheses and statistical analyses, given the possibility of performing meta-analyses.

It is important that the working group can have access to clinical professionals or patient representatives, in order to give their perspective when defining the clinical question or to be consulted during the elaboration process.

2.2. Management of conflict of interest

Potential conflict of interests within the members of an evidence report working group should be carefully identified and duly addressed, following the indications established in WP-A of the TENDER.

3. Planning and protocol elaboration

Protocol preparation is a key phase, since it requires a first approach to the intervention, health technology or technique. Through the protocol the objectives and methods that will be used for the elaboration of an evidence report should be clearly specified. Below is a detailed description of the information that a protocol should contain.

The protocol is the document that provides a detailed description regarding a project, in order to establish the methodological framework, as well as promoting transparency and communication between the parties involved and reducing the risk of bias in the systematic review.

All the working group members should have an active role in developing the protocol. This should include the following sections ²:

3.1. Introduction and aims

It includes the most relevant contextual factors and rationale for the development of the evidence report.

- A description of the condition to be addressed, the background and the knowledge gap that the report intends to cover must be detailed.
- The objectives, both general and specific, of the development of the report must be defined. Clarify what is the utility or benefits of its elaboration.
- The research question should be defined. PICO is a useful format for asking focused clinical questions.

3.2. Methods

Aspects related to how the evidence report question will be answered should be taken into account and properly described in the protocol. Therefore, it is important to indicate the methods that will be followed to obtain, review and interpret the available evidence. Therefore, the following should be stated:

- Information sources that are planned to be consulted, together with the general terms that will be included in the systematic search and time horizons. It should also be indicated whether additional manual searches that will be carried out.
- Inclusion and exclusion criteria must be defined for the selection of evidence.
- Description of the method that will be used to assess the risk of bias of the selected studies.
- It should be indicated whether statistical analyses (meta-analyses) for pulling the effect sizes are to be carried out, or under what conditions they will be developed.

3.3. Organisation and schedule

These are fundamental elements to achieve evidence report objectives:

- Aspects related to the project participants should be included. For example, the working group profiles, etc.
- It is recommended that a detailed schedule with the milestones expected in the development of the report is included in the protocol.

3.4. External review

- The external review procedure that is planned to be followed must be described, as well as the profile and number of reviewers.

4. Developing the Evidence-Based Report

4.1. How to Structure an Evidence-based Report

All the steps that have been planned in the protocol must be carried out and reflected in the content of the evidence report. In this way, in line with the elements to be included in the protocol, the following structure is proposed ³:

- Introduction and justification (also called Background).
- Aim
- Methods
- Results
- Discussion
- Conclusions

4.2. Introduction and justification

Description of the problem and its importance (prevalence, severity, cost implications, impact on function, aesthetics, etc.). Table 1 provides a list of questions to address when defining the introduction and justification of an evidence report ².

- When describing the health problem or condition in which the report is framed, quantitative and qualitative information (prevalence, etc.) and the characteristics of the patients who will constitute the target population must be provided.

- Additionally, in this section, the reason for developing the report must be indicated, describing what is the existing knowledge gap, other approaches that have been previously carried out and how the report is expected to provide the necessary information.

Table 1. Information to include in the introduction section

Elements	Questions/Information to answer within the introduction
Health problem or condition	What is the condition under study (definition)? What are the risk factors for the condition (if applicable)? What is the natural history of the disease? What are the most relevant symptoms or burdens for the patient and family/caregivers? What are the social burdens or considerations to take into account in the analysis of the condition?
Current management of the condition	Currently, what is the diagnostic/therapeutic management of the condition?
Target population	What is the population affected by the condition? Approximately how many patients make up the target population in the context of ERN?
Characteristics of the intervention	What does the intervention and its comparators consist of? What is your mode of action or how would this intervention add value? What are the associated benefits and risks? What is the current level of use of the intervention in the context of ERN? What knowledge needs exist about the intervention?

4.3. Aim

Description of the question to be answered in a format that can be searched. Hypotheses are sometimes also included.

4.3.1. Scope

- Both aspects to be covered and the aspects not covered must be specified. That is, indicate the target population, the focus of the report (prevention, diagnosis, treatment, etc.), setting, etc. Although sometimes the aspects not covered are complementary to those to be covered by the report, it must be clearly indicated in order to delimit the scope. For example, the explicit exclusion of certain age groups.

4.3.2. Research question

- The four parts of the research question should be indicated using PICO format (patients, interventions, comparators, outcomes) (Table 2) ^{2,4}.
 - Additionally, the study designs to review can be an aspect to include in the research question (PICOS).

Table 2. Key elements in PICO questions

PICO aspects	Description
Patients	- Describe the disease or condition of interest. It may be helpful to use broad definitions of population by incorporating closely related disease entities, especially for those rare diseases that do not have a clear diagnostic criterion ⁴ . - Describe the target population, indicating to possible limitations in relation to factors such as age, risk or severity. - Describe the use of the intervention in the population of interest and the clinical context. For example, diagnosis, treatment.
Intervention	- Describe the healthcare intervention or technology in as much detail as possible. For those interventions without a consistent pattern of practice or not used in a consistent way, a broad definition may be an adequate approach. For example, class of medication instead of a particular medication ⁴ .
Comparator	- Select comparators: other health technology, usual treatment, or no treatment, including the rationale for the choice. Usually there is only one treatment option and the use of placebo for comparison is not ethical due to severe course of an untreated disease ⁴ .
Outcomes	- Select the most suitable outcome variables for the assessment. The use of surrogate outcomes may be problematic because there is no clear link between them and patient important outcomes.

Study design (optional)	- Specify the study designs that will be considered and differentiate whether they will be studies of diagnostic performance, efficacy, safety, etc.
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4.3.3. Selection and classification of outcome variables

Evidence reports should analyse all potential patient-important outcomes, including those that are meaningful to the intended users (clinicians, patients, policy makers, etc.).

- Outcomes used to assess both adverse effects as well as beneficial effects are addressed, these may include survival, clinical events, behavioural outcomes, patient-reported outcomes, adverse events, burdens or restrictions on lifestyle and economic outcomes ⁵.
- It is critical that outcomes used to assess adverse effects as well as outcomes used to assess beneficial effects are among those addressed by a review.
- Using surrogate outcomes should be considered only when high-quality evidence regarding important outcomes is lacking.

Core outcome sets have been established to inform researchers, often based on usefulness in decision making and importance to patients and healthcare professionals (see the COMET Initiative for a database of known core outcome sets) ⁶.

4.4. Methods

Search strategy used to collect the evidence should be describe along with the criteria used to include or exclude evidence and the approach to assess the quality of the studies collected ⁷. This information is described in more detail in the Handbook #4: Methodology for the elaboration of CPGs for rare diseases.

4.4.1. Literature search and identification of the evidence

A key step in the elaboration of an evidence report is the identification of the literature. A systematic search for evidence should be carried out. The main aspects to consider are as follows ⁸:

4.4.1.1. Selection of the information sources

Searches should cover at least the core databases, rare diseases-specific databases and other sources:

- Major medical databases such as Embase and Pubmed/MEDLINE, to identify original studies (clinical trials and observational studies) or systematic reviews, etc.
- Depending on the condition to be analysed, it may be useful to consult specific databases (PsycINFO, CINAHL, etc.).
- Specific databases and repositories on rare diseases should be consulted (Orphanet, EURORDIS, etc.)
- Cochrane Library or CRD databases could be a systematic review-specific resource.
- CPGs or Health Technology Assessment (HTA) reports can be important sources of information, so it is useful to search in guideline repositories (GuíaSalud, G-I-N, etc.) and HTA databases.
- Other sources such clinical trials registries can be useful to find ongoing research (European Union Trials Register, ClinicalTrials.gov, WHO International Clinical Trials Registry Platform).
- Rare disease patient registries and databases could provide long-term outcome data in a real-world setting.
- Since information on rare diseases is often scarce and can be found outside of traditional sources, grey literature databases (via Opengrey, etc.) and hand-searching through medical journals is recommended.

Table 3 provides a list of major databases and information sources for literature search:

Table 3. Information sources

Information sources	Access
Systematic reviews	
Cochrane Database of Systematic Reviews (CDSR)	https://www.cochranelibrary.com/
Health Technology Assessment Database (HTA)	https://www.crd.york.ac.uk/CRDWeb/
Database of Abstracts of Reviews of Effectiveness (DARE) (documents produced until March 2015)	https://www.crd.york.ac.uk/CRDWeb/
Tripdatabase	https://www.tripdatabase.com/
PROSPERO (International Prospective Register of Systematic Reviews)	https://www.crd.york.ac.uk/PROSPERO/
Clinical Practice Guidelines	
GuíaSalud	http://www.guiasalud.es/
ECRI	https://guidelines.ecri.org/
G-I-N international guideline library	https://g-i-n.net/library/international-guidelines-library
Tripdatabase	https://www.tripdatabase.com/
Original studies	
Pubmed/MEDLINE	https://pubmed.ncbi.nlm.nih.gov/
Embase	https://www.embase.com/
Rare diseases specific databases	
Orphanet	https://www.orpha.net/
EURORDIS	https://www.eurordis.org/
NORD (National Organisation for Rare Disorders)	https://rarediseases.org/
RARE-BestPractices	http://www.rarebestpractices.eu/
Gene Reviews	https://www.ncbi.nlm.nih.gov/books/NBK1116/
Specific databases for psychology and nursing	
PsycINFO	https://www.ebsco.com/
CINAHL	https://www.apa.org/pubs/databases/psycinfo/
Economic Evaluations	
NHS EED (Economic Evaluation Database) (documents produced until March 2015)	https://www.crd.york.ac.uk/CRDWeb/
Clinical trials registries	
European Union Trials Register	https://www.clinicaltrialsregister.eu/
ClinicalTrials.gov	https://clinicaltrials.gov/
WHO International Clinical Trials Registry Platform	https://apps.who.int/trialsearch/
Grey literature	
Opengrey	http://www.opengrey.eu/

4.4.1.2. Search strategy design

Below are some basic guidelines for creating a comprehensive search strategy:

- Key words should be identified for each of its components (population, intervention, comparator and outcome when using the PICO framework).
- Both free-text and subject headings (Medical Subject Headings (MeSH) and Emtree) should be used.
- The search strategy can be a combination of these search terms by applying boolean logical operators such as AND, OR and NOT across the fields of the search (title, abstract, keywords).
- Searches should aim for high sensitivity, that is identifying all or almost all studies and mitigate the risk of omitting significant evidence.
- Published, highly sensitive, validated search strategies (filters) to identify literature should be considered. The most comprehensive listing of available search filters can be found on the InterTASC Information Specialists' Sub-Group (ISSG) website.
- Additional limits on the publication language, publication period, etc. can be applied to the search.
- For review authors, alerts are a useful tool to monitor what is being published regarding the review topic after the original search has been conducted.

In addition to conducting the search, evidence reports must include an annex where the details related to the strategy are detailed, the following information must be provided:

- Databases searched (source and provider, e.g. MEDLINE/PubMed).
- Exact search strategy employed in each database.
- Any limits or filters applied.
- Exact date of the search.
- Number of records retrieved from each database.

4.4.2. Study selection and data extraction

The scope of a review is defined by the patients, interventions (and comparisons), and outcomes that are of interest (PICO). These components of the question, with the additional specification of types of study that will be included, form the basis of the eligibility criteria for the review.

The process for selecting studies for inclusion in an evidence report should be as follows:

- Search results from different sources should be merged using reference management software.
- Titles and abstracts should be screened to remove obviously irrelevant studies. After that, the full text copy of the potentially relevant studies should be retrieved and examined for compliance with eligibility criteria.
- The review team should make final decisions on study inclusion and proceed to data collection.

Both the study selection process and data extraction should ideally be carried out by two or more working group members (peer review). Once the studies to be included have been selected, for the information extraction these key points should be considered:

- It is recommended to use forms to collect enough and unambiguous data that represent the original in a structured and organised manner. This form should allow future access and data sharing
- If a meta-analysis or some other type of statistical analysis for pulling effect sizes is considered, effort should be made to identify data needed from studies. These data often need to be calculated or converted from data reported in the original studies.

4.4.3. Certainty of the evidence (GRADE)

The GRADE approach specifies four levels of the certainty of the evidence for a given outcome: high, moderate, low and very low. Authors should follow a judgement process that operates within a transparent structure. Hence, assessments of certainty are determined through consideration of five domains: risk of bias, inconsistency, indirectness, imprecision and publication bias. Certainty of the evidence can be reduced or increased according to this assessment⁹. Below is a description of these five domains and their valuation:

4.4.3.1. Risk of bias

Confidence in an effect estimate decreases when studies suffer from limitations that are likely to result in a biased assessment of the intervention effect.

There are different systems to assess the risk of bias from studies that assess both clinical results (safety and effectiveness), patient's preferences (qualitative evidence), as well as studies that analyse economic impact or cost-effectiveness.

Tools or instruments for evaluating the quality of the evidence that are considered most relevant are described below:

Systematic reviews

One of the most widely used scales for assessing methodological quality is the *Assessment of Multiple Systematic Reviews (AMSTAR-2)* tool, consists of 16 items and is used for clinical trial reviews and observational studies. An online version of the quality checklist is available on the AMSTAR website¹⁰.

Randomised clinical trials

Risk of Bias (RoB 2) instrument is the recommended tool to assess the risk of bias in randomised trials. It is structured into a fixed set of domains, focussing on different aspects of trial design, conduct, and reporting. The domains included in RoB 2 cover all types of bias that are currently understood to affect the results of randomised trials¹¹. These are:

- bias arising from the randomisation process;
- bias due to deviations from intended interventions;
- bias due to missing outcome data;
- bias in measurement of the outcome; and
- bias in selection of the reported result.

According to the answers to a series of questions (signalling questions), a proposed judgement about the risk of bias is generated by an algorithm.

Non-Randomised studies

The *Risk Of Bias In Non-randomized Studies of Interventions* (ROBINS-I) tool is recommended for assessing risk of bias in a NRSI: it provides a framework for assessing the risk of bias in a single result (an estimate of the effect of an experimental intervention compared with a comparator intervention on a particular outcome). Many features of ROBINS-I are shared with the RoB 2 tool for assessing risk of bias in randomised trials^{12, 13}. The *Newcastle-Ottawa Scale* is also recommended for assessing the quality of nonrandomised studies¹⁴.

Diagnostic test studies

For the risk of bias assessment in diagnostic tests studies, the *Quality Assessment of Diagnostic Accuracy Studies* (QUADAS-2) tool could be used. This is made up of 4 domains: patient selection, index test evaluated, reference standard and patient flow, and timing of the test. Each is assessed in terms of risk of bias and the first three in terms of concerns regarding applicability. Signalling questions are included to assist in judgements about risk of bias¹⁵.

Economic Evaluations

Critical appraisal of health economics studies can be informed by the use of checklists that have been developed to guide assessments of methodological quality. Whilst no checklists have been formally validated, two have received more scrutiny than most:

- *British Medical Journal Checklist* for authors and peer reviewers of economic submissions¹⁶;
- *Consensus on Health Economic Criteria* (CHEC) list for assessment of methodological quality of economic evaluations¹⁷.

Qualitative evidence

Qualitative evidence synthesis can add value by providing decision makers with additional evidence to improve understanding of intervention complexity, contextual variations, implementation, and stakeholder preferences and experiences¹⁸. The use of the *Confidence in the Evidence from Reviews of Qualitative research* (CERQual) tool is proposed to assess how much confidence to place in findings from qualitative evidence. It is based in four aspects:

- the methodological limitations of the qualitative studies contributing to a review finding,
- the relevance to the review question of the studies contributing to a review finding,
- the coherence of the review finding, and
- the adequacy of data supporting a review finding¹⁹.

Case series

In the case of rare diseases, a large number of case series studies may be identified through the search. They should be assessed for risk of bias. Hence, it is recommended to use specifically designed scales, such as The Quality Appraisal Checklist for Case Series of the Institute of Health Economics ²⁰.

Consensus statements

Consensus are not a main source of evidence, however, in the field of rare diseases, they can be useful to know what the patient management for certain conditions is, when no evidence is available. For this reason, consensus may be included in the narrative synthesis, without being part of the statistical analyses for effect size estimation. These consensus statements should be taken with caution considering their high risk of bias. A number of strategies for eliciting and synthesizing when there is lack of high certainty evidence have been proposed ²¹.

4.4.3.2. Inconsistency

The existence of variability or heterogeneity in the results of the different included studies for a certain outcome variable. This may be due to differences in population included, interventions, outcomes, or study design ²².

4.4.3.3. Imprecision

It occurs when the confidence intervals are wide, the samples are small, or the events are few. For example, if the confidence interval crosses the threshold established to recommend an intervention or not, the quality of the evidence falls due to imprecision, regardless of the value of the estimator ²³.

4.4.3.4. Publication/Reporting bias

Investigators often fail to report studies on the basis of results (typically those that show no effect: publication bias) or outcomes (typically those that may be harmful or for which no effect was observed: selective outcome non-reporting bias). If a large number of studies included in the review do not contribute to an outcome, the certainty of the evidence may be downgraded ²⁴.

4.4.4. Evidence synthesis

This judgment process that is carried out on the quality and certainty of the body of evidence must be correctly reflected ²⁵. Synthesis can be done from a qualitative or quantitative point of view.

When conducting a qualitative synthesis:

- It is recommended to give a description the clinical and methodological characteristics of the included studies, including their size, inclusion or exclusion of important subgroups, timeliness and other relevant factors.

In addition to a qualitative synthesis. There are multiple manuals and tutorials for the development of meta-analyses detailing the specific process ²⁶. The report may include a quantitative analysis considering the following:

- Use expert methodologist to develop, execute and peer review the meta-analysis
- All estimates obtained must be accompanied by their corresponding measures of statistical uncertainty.
- The heterogeneity among study effects should be addressed using appropriate weighted technique to combine study results.
- Additionally, causes of any heterogeneity should be investigated and addressed, if possible, conducting sensitivity analyses.

4.5. Results

The results section should be made up of a brief narrative and structured summary of the studies assessed, including their design, main characteristics, and effect estimators for each variable of interest. The number of studies evaluating each outcome and the estimated effect must be reported. Finally, the certainty of the evidence and

reasons for upgrading/downgrading for each of the outcome evaluated must be included with its confidence interval.

GRADE methodology proposal for the presentation of the results is the Summary of Findings (SoF) table. For a given comparison of interventions, SoF table provides key information concerning the magnitudes, the amount of available evidence and the certainty (or quality) of available evidence. Specifically, it must contain the following information ⁹:

- Population and setting addressed by the available evidence.
- Comparison addressed in the SoF, including the intervention and comparator interventions
- Critical or important health outcomes, both desirable and undesirable.
- Absolute and relative magnitude of effect measured for each
- Numbers of participants and studies contributing to the analysis of health outcomes
- GRADE assessment of the overall certainty of the body of evidence for each outcome

In the event that meta-analyses have been performed, authors should consider presenting results in a format that is easy to interpret. For example, using forest plots to help on the interpretation of odds ratios and standardized mean differences.

4.6. Discussion and conclusions

Review authors should not make recommendations about healthcare decisions, but they can highlight different factors that are relevant for EBR users and may be considered when determining a decision ²⁵.

- Description of the strengths and limitations of individual studies and patterns across studies.
- Description, in plain terms, on how flaws in the design or execution of the study (or groups of studies) could bias the results, explaining the reasoning behind these judgments.
- Description about the relationship between the characteristics of the individual studies and their reported findings and patterns across studies
- Discussion the relevance of individual studies to the population, comparisons cointerventions settings and outcomes or measures of interest.

5. External review

It is a fundamental process in the elaboration of an evidence report that will enrich its content, increasing its external validity and facilitating its acceptance by its end users ⁷.

- External reviewers should have multidisciplinary profiles. It may include clinical experts from the ERN, methodological and technical experts, end-users, and individuals affected by the condition addressed in the report.
- If important perspectives and stakeholders are missing from the evidence report, these should be represented in the external review group. For example, policy makers.
- Basic information about the evidence report, including the name, the scope and purpose, the organisations funding and developing it should be detailed in the request for external reviewers.
- The scope of the external review, including any specific questions asked to answer should be indicated. It is recommended to prepare an external review form, so that the reviewers' responses are collected in a homogeneous way.
- External reviewers should be subject to the declaration of interest policy.

Key issues

It is essential to gather a multidisciplinary working group for the development of Evidence Reports.

Protocol elaboration is a key part on the development of an evidence report, which will determine the research question, scope, objectives and methods that will be used.

The main steps for the elaboration of an evidence report are:

- search and identification of evidence
- study selection
- evaluation of methodological quality
- synthesis of evidence
- presentation of results and conclusions

Finally, the process ends with an external review by different stakeholders and potential users.

Abbreviations

AMSTAR-2	A Measurement Tool to Assess Systematic Reviews-2
CDST	Clinical Decision Support Tool
CERQual	Confidence in the Evidence from Reviews of Qualitative research
CHEC	Consensus on Health Economic Criteria
CPG	Clinical Practice Guideline
EC	European Comission
ERN	European Reference Networks
FPS	Fundación Progreso y Salud
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HTA	Health Technology Assessment
IACS	Aragon Health Sciences Institute (Instituto Aragonés de Ciencias de la Salud)
InterTASC-ISSG	InterTASC Information Specialists' Sub-Group
QUADAS-2	Quality Assessment of Diagnostic Accuracy Studies-2
RoB 2	Risk of Bias 2
ROBINS-I	Risk of Bias In Non-randomized Studies of Interventions-I
SoF	Summary of Findings
WP	Work Package

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